Relevance of Abusive Head Trauma to Intracranial Hemorrhages and Bleeding Disorders

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Abstract

BACKGROUND—Bleeding disorders and abusive head trauma (AHT) are associated with intracranial hemorrhage (ICH), including subdural hemorrhage (SDH). Because both conditions often present in young children, the need to screen for bleeding disorders would be better informed by data that include trauma history and are specific to young children. The Universal Data Collection database contains information on ICH in subjects with bleeding disorders, including age and trauma history. Study objectives were to (1) characterize the prevalence and calculate the probabilities of any ICH, traumatic ICH, and nontraumatic ICH in children with congenital bleeding disorders; (2) characterize the prevalence of spontaneous SDH on the basis of bleeding disorder; and (3) identify cases of von Willebrand disease (vWD) that mimic AHT.

METHODS—We reviewed subjects <4 years of age in the Universal Data Collection database. ICH was categorized on the basis of association with trauma. Prevalence and probability of types of ICH were calculated for each bleeding disorder.

RESULTS—Of 3717 subjects, 255 (6.9%) had any ICH and 206 (5.5%) had nontraumatic ICH. The highest prevalence of ICH was in severe hemophilia A (9.1%) and B (10.7%). Of the 1233 subjects <2 years of age in which the specific location of any ICH was known, 13 (1.1%) had

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spontaneous SDH (12 with severe hemophilia; 1 with type 1 vWD). The findings in the subject with vWD were not congruent with AHT.

CONCLUSIONS—In congenital bleeding disorders, nontraumatic ICH occurs most commonly in severe hemophilia. In this study, vWD is not supported as a "mimic" of AHT.

Abusive head trauma (AHT) is the leading cause of fatalities from child abuse.[1] Intracranial hemorrhage (ICH), specifically subdural hemorrhage (SDH), in a young child with a history of minimal or no trauma is highly concerning for AHT.[2] Children with congenital bleeding disorders may present similarly to children with AHT.[3-5] Incorrectly diagnosing abuse could result in inappropriately removing a child from a home. Further morbidity could occur because of failure to identify a preexisting bleeding disorder. However, failing to accurately diagnose abuse often results in further harm to a child.[6] It is critical to appropriately evaluate for congenital bleeding disorders in the setting of possible AHT.

The American Academy of Pediatrics (AAP) published recommendations for evaluating for bleeding disorders in the setting of possible AHT.[4,5] The included testing strategy was based on the probability of an ICH occurring in a child with a given congenital bleeding disorder. These probability calculations were based on the prevalence of various bleeding disorders and the prevalence of ICH within those individual bleeding disorders. For example, the probability of an individual in the general population having an ICH because of factor XIII deficiency can be calculated by using the estimated prevalence of the condition (1 in 2 million people) and the prevalence of ICH within the population with the condition (33%)[5]:

$$\text{(prevalence of Factor XIII deficiency)} \times \text{(prevalence of ICH in subjects with Factor XIII deficiency)}$$
$$= (1 \text{ in } 2 \text{ million}) \times (1/3) = 1 \text{ in } 6 \text{ million} .$$

Authors of the majority of previous studies characterizing ICH in congenital bleeding disorders did not focus on young children. The authors of these studies primarily considered the lifetime risk of ICH, and many bleeding disorders, such as von Willebrand disease (vWD), have no specific published data regarding prevalence of ICH. Moreover, the authors of most of these previous studies did not differentiate SDH from other types of ICH or separate traumatic from nontraumatic ICH.[5] Spontaneous ICH, particularly spontaneous SDH, from a bleeding disorder may be confused with AHT. Furthermore, clarification of the role of vWD in the generation of spontaneous SDH is critical because court decisions have been altered on the basis of the suggestion that vWD causes findings that mimic AHT.[7]

The Universal Data Collection (UDC) database of the Centers for Disease Control and Prevention contains specific information on ICH and SDH in subjects with congenital bleeding disorders. Subjects with bleeding disorders who received care from 1998 to 2011 in federally funded hemophilia treatment centers (HTCs) are included.[8] Patients with bleeding disorders of any severity or type could be referred to the HTCs by their primary care providers or by self-referral. Subjects who consented for data collection were entered into the database by the HTC providers at the time of their visit. Only those patients with bleeding disorders who were seen at HTCs were eligible to be entered into the database. As of 2003, children <2 years of age were eligible for more frequent and detailed data collection that included specific details such as location of ICH (eg, subdural), birth

complications, and trauma. Provided in the UDC database is an opportunity to assess for associations of specific types of ICH with specific types of circumstances. By using the UDC data set of subjects <4 years of age, our objectives with this study were to (1) calculate the prevalence and probabilities of any ICH, traumatic ICH, and nontraumatic ICH for all and specific congenital bleeding disorders; (2) characterize the prevalence of spontaneous SDH on the basis of bleeding disorder; and (3) identify cases of vWD in which AHT is mimicked.

METHODS

Data Source

We performed a retrospective analysis of subjects <4 years of age in the UDC database. Details of the database and collection methods have been previously published.[9,10] A network of HTCs receives federal support to provide clinical care for patients with hemophilia and other bleeding disorders. People with bleeding disorders receiving care in HTCs were eligible to participate in the UDC system from May 1998 until September 2011. The data from a total of 146 geographically distributed HTCs in the United States were contributed to the UDC during the study period. Details on UDC-participating centers are available at the following Web site: https://www2a.cdc.gov/ncbddd/ htcweb/Dir_Report/ Dir_Search. asp. Approximately 70% of people with hemophilia in the United States receive care in these comprehensive clinics.[9]

Study Population

Subjects with bleeding disorders enrolled in the UDC before the age of 4 and who had at least 1 completed annual visit or infant visit form were included. When >1 episode of ICH occurred, the first recorded ICH was used because subjects with known bleeding disorders and multiple episodes of ICH are unlikely to be confused with victims of AHT. Eligible diagnoses included hemophilia A or B (all severities); all types of vWD; deficiencies of factors VII, XI, and XIII; acquired hemophilia; combined factors V and VIII; factors I, II, V, X, XII; and platelet disorders. The diagnoses of bleeding disorders and severities were reported by the submitting HTC. Subjects with combined deficiencies (other than factors V or VIII), hemophilia of unknown severity level, and those with vWD of unknown type were excluded. Subjects with inhibitors were also excluded because these subjects would be known to have a bleeding disorder and are not likely to be confused with AHT. Informed consent was obtained from the parents of all subjects. The study was approved by each participating center's institutional review board.

Data Collection

A registration form was used to collect demographic and initial data. Subjects were deidentified and assigned a number that was linked back to the submitting HTC. Demographic information included age, race and/or ethnicity, and medical insurance type. Data on bleeding disorder diagnosis, age at diagnosis, age at first bleed, and location of first bleed were included. Further data were collected by using an "annual visit" or "baby visit" form.

Annual Visit Form—An annual visit form was used to collect data on all UDC participants >2 years of age from 1998 to 2011. Beginning in 2003, data on subjects <2 years of age were collected by using a baby visit form (see below) until they turned 2 years old, after which data from subsequent visits were collected by using the annual visit form. Data were collected by HTC staff during clinic visits and included the occurrence of any ICH since the previous annual visit, age of subject at the time of ICH, and whether the ICH was associated with "trauma," "thrombocytopenia," or "other." For the purposes of this study, ICH that was coded as any of the choices besides "trauma" was classified as "nontraumatic." The annual visit form did not include location of ICH.

Baby Visit Form—This form was completed at each subject's first visit to the HTC (if the subject was <2 years of age) and at visits occurring as frequently as every 6 months thereafter until the subject reached 2 years of age. The baby visit form included the location (subdural, epidural, subarachnoid, intra- or periventricular, or cerebellar) of ICH and whether the episode was associated with "trauma," "delivery," "thrombocytopenia," "a medical procedure," was "spontaneous," or "other." To combine data from the baby visit form and the annual visit form to address the first objective of the study, we classified an ICH as nontraumatic if any of the choices besides trauma were selected.

Data Analysis

In Fig 1, we describe the use of information from the baby visit and annual visit forms in this study. Descriptive statistics were used to characterize the subjects.

Traumatic and Nontraumatic ICH—Diagnostic confusion with AHT is most likely to occur from bleeding disorder-associated ICH that is nontraumatic in nature or attributed to minor trauma.[4] As such, the occurrences of nontraumatic ICH from the annual visit and baby visit forms were combined and tabulated, as were the traumatic ICH from both forms.

Prevalence and Probability of ICH Based on Bleeding Disorder—Prevalences for the categories of ICH (any, traumatic, and nontraumatic) were calculated from the UDC data. To determine the probability of ICH within specific bleeding disorders, we determined the prevalence of each bleeding disorder using the published registries as previously described in the AAP technical report.[5] As described in the AAP technical report, the upper limits of published condition prevalence were used to provide the upper limit of probability of ICH associated with a given bleeding disorder. Additionally, age-adjusted prevalences for all subjects with hemophilia and severe, moderate, and mild hemophilia were calculated from previously published data.[9] The probabilities of any, traumatic, and nontraumatic ICH occurring in association with a given bleeding disorder were calculated by using the previously identified prevalence of the specific bleeding disorder, with the exception of the age-adjusted prevalences for hemophilia[5]:

(prevalence of bleeding disorder $\times$ (prevalence of any, traumatic, or nontraumatic ICH in subjects, with a given bleeding disorder) = (probability of an individual in the general population having any, traumatic, or nontraumatic ICH occurring with a given bleeding disorder)

In addition to contributing to the above determinations of prevalence and probability of ICH based on bleeding disorder, subjects with a complete baby visit form were analyzed separately because of greater detail in available data. Subjects were again classified on the basis of bleeding disorder but also on ICH (in general) or SDH (specifically) on the basis of the presence of trauma or spontaneous etiology.

RESULTS

A total of 3717 subjects <4 years of age were enrolled in the UDC data set during the study period. Because of the genetics of hemophilia, the subjects were overwhelmingly male. Further characterization of the study population is in Table 1. Although vWD is the most common bleeding disorder, with low von Willebrand factor levels occurring in up to 1% of the population,[5] it was underrepresented in the UDC data set because ~5 times more subjects with hemophilia than vWD were included. More severe bleeding disorders were diagnosed at younger ages.

Table 2 contains the prevalences and probabilities of various types of ICH within specific bleeding disorders for all subjects, including combined data from both the annual visit and baby visit forms. There were not enough individuals in the database with factors I, II, V, and X deficiencies or platelet disorders to be evaluated separately, so these subjects were combined into "All other bleeding disorders." Of all subjects, 255 (6.9%) had any ICH, 206 (5.5%) had nontraumatic ICH, and 49 (1.3%) had traumatic ICH. The probability of any ICH occurring was >1 in 1 million in only the following 3 conditions: severe hemophilias A and B and vWD. The probability of an ICH occurring in vWD was highest because of the relatively high prevalence of vWD. Conversely, factor XIII deficiency has a high prevalence of associated ICH, but the rarity of the condition results in a low probability that an individual in the general population would have an ICH because of this condition.

Table 3 contains data from subjects <2 years of age with at least 1 completed baby visit form. Of the group with baby visit form data (n = 1233), 84 (6.8%) had any ICH before the age of 2, 12 (1.0%) had a traumatic SDH, and 13 (1.1%) had a spontaneous SDH. Approximately 1% of subjects with hemophilia A or B had a spontaneous SDH, all of whom had severe hemophilia. The probability of a spontaneous SDH in severe hemophilia A and severe hemophilia B was ~1 in 1.1 million and 1 in 4.8 million, respectively.

Detailed information on the subject with a spontaneous SDH and type 1 vWD was obtained from the treating HTC. The subject presented at 4 months of age with "body stiffening." A head computed tomography scan done at the time (Fig 2) revealed bilateral SDH with layered hyperdense and hypodense components on the left. Laboratory tests on this subject included a von Willebrand factor level of 43% and ristocetin cofactor activities ranging from 30% to 43%. Von Willebrand multimers were normal. An ophthalmology examination revealed no retinal hemorrhages, and a skeletal survey revealed no fractures. The child has had no long-term neurologic sequelae. No diagnosis of child abuse was made, and Children's Protective Services did not substantiate the report of maltreatment.

DISCUSSION

With this study, we characterize the association of specific bleeding disorders with traumatic and nontraumatic ICH in children <4 years of age. Furthermore, we assess the occurrence of SDH in bleeding disorders, allowing for a more accurate assessment of the potential for AHT to be mimicked in these conditions.

Several probabilities for any ICH in this study were substantially different from those published by the AAP.[4,5] For instance, in this study, the probabilities of any ICH in a child <4 years of age with hemophilia A and B were 1 in 140 000 and 1 in 465 000, respectively. The previously published probabilities of 1 in 50 000 male patients and 1 in 200 000 male patients were based on studies in which subjects of all ages were included. However, probabilities similar to those previously published were found for deficiencies of factors VII, XI, XIII, and type 3 vWD. Because we included only young children in this study and used age-adjusted disease prevalence for hemophilia subtypes, it is likely that we more accurately represent the true occurrence of ICH. Low numbers of extremely rare disorders, such as deficiencies in factors II, V, or X, prohibited a probability calculation. This is logical because the previously calculated probability of ICH due to those deficiencies were 1 in 10 million, 1 in 10 million, and 1 in 5 million, respectively.[4] This accentuates the low likelihood of confusion of these conditions with AHT.

In cases of suspected AHT, it is common for a history of minor trauma to be offered as the inciting cause of an ICH.[11] In such cases, the data from this study can be used to identify the probability of a bleeding disorder being the cause of the ICH, and these probabilities differ substantially from those for any ICH, regardless of trauma, as revealed in Table 2 (eg, in hemophilia B, it is 1 in 450 000 for any ICH but 1 in 2.6 million for traumatic ICH). The same probability adjustments can be made for reported ICH without a history of trauma in suspected AHT, acknowledging that nontraumatic ICH reported in Table 2 includes ICH associated with birth and medical conditions. As such, these probabilities are overestimates of the true probability of a spontaneous ICH.

The high probability of ICH associated with type 1 vWD was driven by the high prevalence of the condition (0.1% of the population). These data contradict a large body of literature in which authors document that most people with type 1 vWD do not have significant bleeding symptoms until they have a "bleeding challenge," such as dental extraction or surgery, and only 0.01% to 0.1% present with bleeding symptoms.[12] ICH associated with vWD has been rarely reported.[13-17] Although type 1 vWD is known to be ~5 times more common than hemophilia A, there were ~5 times as many subjects with hemophilia A as there were with type 1 vWD seen in HTCs during the study period, likely due to the lack of significant bleeding symptoms in people with type 1 vWD. As such, the calculated probability for ICH from type 1 vWD is likely a significant overestimate.

SDH is the presenting finding of concern in most cases of suspected AHT.[18] Table 3 reveals that SDH is rare but real in congenital bleeding disorders. Spontaneous SDH (as has been hypothesized to occur in alleged misdiagnoses of AHT) was only identified in the following 3 bleeding disorders: severe hemophilia A and B and type 1 vWD. The probabilities of this

occurring in severe hemophilia A or B are exceedingly low, and screening for severe hemophilia A and B is completed with an activated partial thromboplastin time. The patient who was reported to have type 1 vWD does not meet the current diagnostic criteria but was included in the analysis because this was the diagnosis reported by the center.[19] The presentation, nature of SDH, lack of associated findings, and outcome of the single subject with spontaneous SDH and reported vWD does not bear resemblance to acute AHT.[20-22] With our data, vWD is not supported as a mimic of AHT.

This study has several limitations. Only patients seen at HTCs were entered into the UDC data set. The UDC data set is not generalizable to all patients with bleeding disorders. It is likely that patients with more severe bleeding symptoms, including ICH, were more likely to be referred to HTCs. Thus, the probability and prevalence for ICH and/or SDH for each bleeding disorder in this study are likely to be overestimates of the true probability and prevalence. However, given the scope and nature of the UDC data set, it is likely the best available data regarding these issues. With the UDC data set, we cannot verify the exact cause of every ICH, and the severity of reported traumas was not recorded. Also, children with bleeding disorders who die with a first ICH may not be captured in the data set, and recall bias may affect the data set. Additionally, the classification of nontraumatic ICH in this study includes causes such as birth and medical procedures. The data need to be interpreted with the consideration that the probabilities are overestimates of the probability of a true spontaneous or nontraumatic ICH. However, they are likely more accurate than previously reported probabilities that did not make the traumatic versus nontraumatic distinction. Subjects with severe complications, particularly in common but mild bleeding disorders, are likely overrepresented in the UDC data set. Given this consideration, the extremely low actual number of cases of SDH associated with vWD in this study supports the idea that vWD is rarely associated with SDH, and when this does occur, the findings would not be congruent with AHT.[20-22]

In congenital bleeding disorders, nontraumatic ICH, particularly spontaneous SDH, occurs most commonly in severe hemophilia A and B. Previous AAP recommendations included testing for factors VIII and IX in situations concerning for AHT to detect mild or moderate hemophilia. The authors of these data do not support including such testing, particularly in cases with no history of trauma. Finally, vWD is not supported as a "mimic" of AHT.

Acknowledgments

ABBREVIATIONS

AAP	American Academy of Pediatrics
AHT	abusive head trauma
HTC	hemophilia treatment center
ICH	intracranial hemorrhage
SDH	subdural hemorrhage
UDC	Universal Data Collection
vWD	von Willebrand disease

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WHAT'S KNOWN ON THIS SUBJECT

Bleeding disorder-associated intracranial hemorrhage may be confused with abusive head trauma (AHT). Published strategies for testing for bleeding disorders in situations concerning for AHT were based on data that did not consider child age or trauma history.

WHAT THIS STUDY ADDS

This single database study reveals the probability of traumatic and nontraumatic intracranial and, specifically, subdural hemorrhage occurring in young children with specific bleeding disorders. With these data, von Willebrand disease is not supported as a mimic of AHT.
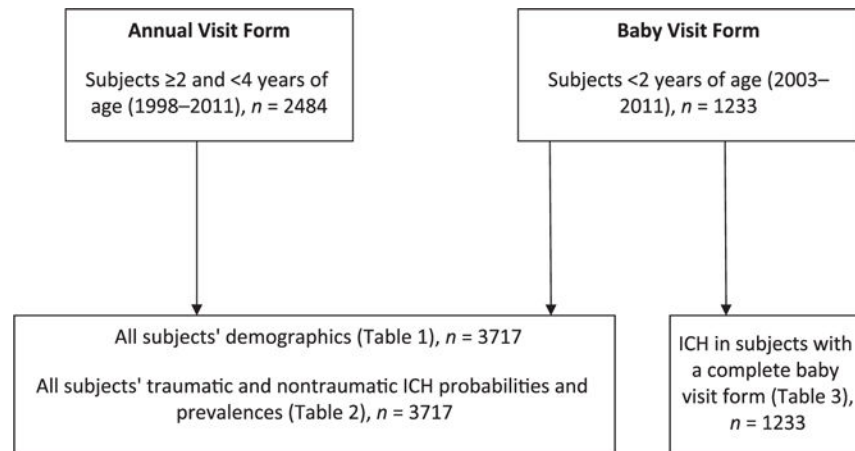
FIGURE 1.
Analysis of study subjects.
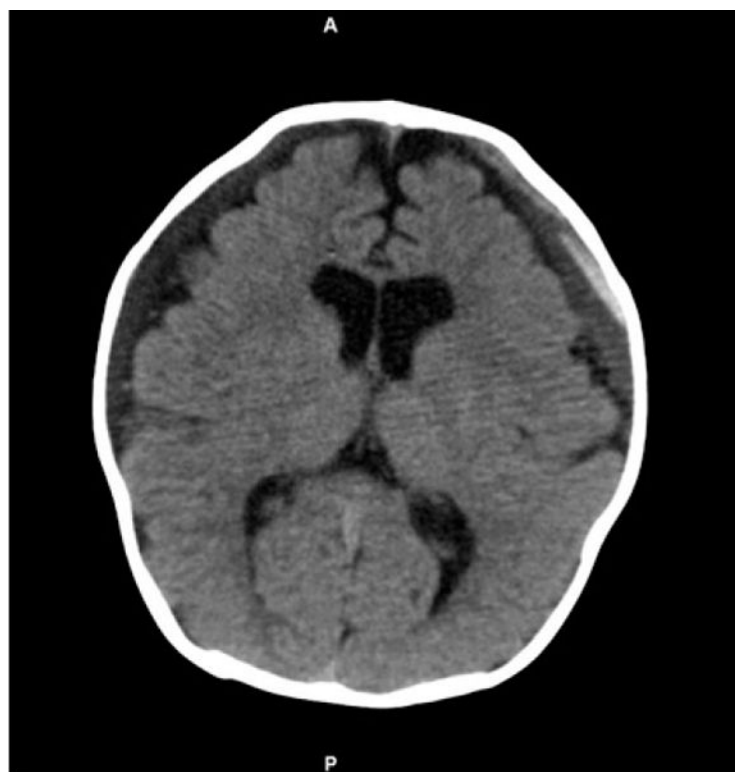
FIGURE 2.
Head computed tomography scan of the single subject with type 1 vWD and spontaneous SDH.

TABLE 1

Demographics of Subjects <4 Years of Age in the UDC Database

	Subjects, *n* (%)	Male Sex, %	White (Non-Hispanic), %	Medicaid, %	Mean Age at Diagnosis, mo
Hemophilia A	2541 (68.3)	98.9	61.3	41.2	3.6
Severe	1635	99.6	59.9	43.5	2.6
Moderate	405	99.3	61.2	40.0	4.5
Mild	501	96.6	66.1	34.9	6.3
Hemophilia B	646 (17.4)	98.0	69.2	69.2	4.5
Severe	280	98.9	59.3	59.3	2.6
Moderate	232	98.3	79.7	79.7	4.9
Mild	134	96	72	72	8
vWD	433 (11.7)	59.1	70.0	40.2	15.7
Type 1	315	59.7	72.1	42.7	18.5
Type 2	81	56	62	34	12
Type 3	37	57	70	31	8
Factor VII deficiency	25 (1)	72	40	40	10
Factor XI deficiency	16 (0)	75	69	6	11
Factor XIII deficiency	10 (0)	60	40	60	3
All other bleeding disorders	46 (1)	72	74	26	7
Total	3717	92.8	63.8	45.6	5.5

TABLE 2

Prevalence and Probability of ICH in All Study Subjects

Bleeding Disorders[a]	Bleeding Disorder Prevalence	Subjects with ICH (%)	Any ICH Probability	Subjects with Traumatic ICH (%)	Traumatic ICH Probability	Subjects with Nontraumatic ICHb (%)	Nontraumatic ICH Probability[b]
Hemophilia A							
All	1 in 9500	178 (7.0)	1 in 140 000	36 (1.4)	1 in 680 000	142 (5.6)	1 in 170 000
Severe	1 in 20 000	148 (9.1)	1 in 220 000	26 (1.6)	1 in 1.25 million	122 (7.5)	1 in 267 000
Moderate	1 in 40 000	16 (4.0)	1 in 1 million	7 (1.8)	1 in 2.2 million	9 (2.2)	1 in 1.8 million
Mild	1 in 30 000	14 (2.8)	1 in 1.1 million	3 (0.6)	1 in 5 million	11 (2.2)	1 in 1.4 million
Hemophilia B							
All	1 in 34 000	49 (7.6)	1 in 450 000	8 (1.2)	1 in 2.6 million	41 (6.4)	1 in 530 000
Severe	1 in 95 000	30 (10.7)	1 in 885 000	3 (1.1)	1 in 8.3 million	27 (9.6)	1 in 990 000
Moderate	1 in 110 000	8 (3.4)	1 in 3.1 million	4 (1.7)	1 in 6.5 million	4 (1.7)	1 in 6.5 million
Mild	1 in 120 000	11 (8)	1 in 1.5 million	1 (1)	1 in 12.5 million	10 (7)	1 in 1.7 million
vWD							
All	NA	16 (3.7)	NA	5 (1.1)	NA	11 (2.3)	NA
Type 1	1 in 1000	12 (3.8)	1 in 26 000	4 (1.3)	1 in 77 000	8 (2.5)	1 in 40 000
Type 2	NA	2 (2)	NA	0 (0)	NA	2 (2)	NA
Type 3	1 in 300 000	2 (5)	1 in 6 million	1 (3)	1 in 11 million[c]	1 (3)	1 in 11 million[c]
Factor VII deficiency	1 in 300 000	4 (16)	1 in 1.9 million	0 (0)	NA	4 (16)	1 in 1.9 million
Factor XI deficiency	1 in 100 000	0 (0)	0	0 (0)	NA	0 (0)	NA
Factor XIII deficiency	1 in 2 million	3 (30)	1 in 6.7 million	0 (0)	NA	3 (30)	1 in 6.7 million
All other bleeding disorders	NA	5 (10.9)	NA	0	NA	5 (10.9)	NA

NA, not applicable.

[a] Diagnosis of bleeding disorder as provided by submitting HTC.

[b] Includes ICH caused by medical interventions, birth, associated medical conditions, and spontaneous ICH.

[c] Of the ICH occurring in type 3 vWD, 50% were nontraumatic. Because of low numbers in the total cohort for this condition, reported prevalence was rounded to the nearest whole number. However, the actual calculated prevalence (without rounding) was used to calculate probabilities.

TABLE 3

Prevalence and Probability of ICH in Subjects <2 Years of Age With Complete Baby Visit Form

Bleeding Disorders	No. Subjects	Subjects With Any ICH (%)[a][b]	Any ICH Probability	Subjects With Traumatic ICH (%)	Traumatic ICH Probability	Subjects With Traumatic SDH (%)	Traumatic SDH Probability	Subjects With Spontaneous ICH (%)	Spontaneous ICH Probability	Subjects With Spontaneous SDH (%)	Spontaneous SDH Probability
Hemophilia A											
All	904	61 (6.7)	1 in 140 000	16 (1.8)	1 in 530 000	8 (1)	1 in 76 000	20 (2.2)	1 in 430 000	10 (1.1)	1 in 860 000
Severe	565	52 (9.2)	1 in 220 000	10 (1.8)	1 in 1.1 million	5 (1)	1 in 2.2 million	19 (3.4)	1 in 590 000	10 (1.8)	1 in 1.1 million
Moderate	140	4 (3)	1 in 1.3 million	3 (2)	1 in 1.9 million	1 (1)	1 in 5.7 million	1 (1)	1 in 5.7 million	0 (0)	0
Mild	199	5 (2.5)	1 in 1.2 million	3 (1.5)	1 in 2 million	2 (1.0)	1 in 3 million	0 (0)	0	0 (0)	0
Hemophilia B											
All	219	16 (7.3)	1 in 465 000	3 (1.4)	1 in 2.4 million	2 (0.9)	1 in 3.8 million	6 (2.7)	1 in 1.3 million	2 (0.9)	1 in 3.8 million
Severe	103	11 (11)	1 in 860 000	1 (1)	1 in 9.5 million	0 (0)	0	4 (4)	1 in 2.4 million	2 (2)	1 in 4.8 million
Moderate	80	3 (4)	1 in 2.9 million	2 (3)	1 in 4.4 million	2 (3)	1 in 4.4 million	1 (1)	1 in 8.8 million	0 (0)	0
Mild	36	2 (6)	1 in 2.1 million	0 (0)	0	0 (0)	0	1 (3)	1 in 4.3 million	0 (0)	0
vWD											
All	81	3 (4)	NA	2 (2)	NA	2 (2)	NA	1 (2)	NA	1 (1)	NA
Type 1	59	2 (3)	1 in 29 000	1 (2)	1 in 59 000	1 (2)	1 in 59 000	1 (2)	1 in 59 000	1 (2)	1 in 59 000
Type 2	14	0 (0)	NA	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0
Type 3	8	1 (13)	1 in 2.4 million	1 (13)	1 in 2.4 million	1 (13)	1 in 2.4 million	0 (0)	0	0 (0)	0
Factor VII deficiency	6	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0
Factor XI deficiency	4	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0
Factor XIII deficiency	4	3 (75)	1 in 2.7 million	0 (0)	0	0 (0)	0	3 (75)	1 in 2.7 million	0 (0)	0
All other bleeding disorders	15	1	NA	0 (0)	NA	0 (0)	NA	0 (0)	NA	0 (0)	NA
Total	1233	84 (6.8)	NA	21 (1.7)	NA	12 (1.0)	NA	31 (2.5)	NA	13 (1.1)	NA

NA, not applicable.

[a] Includes subjects with spontaneous ICH and ICH due to delivery, trauma, medical procedures, thrombocytopenia, and other causes. Therefore, the number of subjects with ICH due to trauma and with spontaneous ICH does not summate to the number of total subjects with ICH.

[b] Subjects with ICH includes subjects with all forms of ICH, including SDH.